REMARKS

Claims 1-49 are pending in the instant application. Claims 6-9, 17, 18, 26-29, 37, 38 and 41-48 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 have been examined on the merits.

Claim 49 has now been canceled with this response. Applicants respectfully reserve the right to pursue subject matter given up with this cancellation at a later date.

As discussed further below, claims 3-5, 15, 16, 23-25, 35 and 36 are currently unexamined claims, corresponding to unelected species, that have not been withdrawn from consideration. Applicants expect that, upon a finding that the elected species are patentable, they will be entitled to a further search of these species and the corresponding claims.

Also as discussed further below, Applicants note that claims 6-9, 17, 18, 26-29, 37, 38, and 41-48 have been withdrawn from consideration, but are related to the elected invention by linking claims 1 and 21. Accordingly, should linking claims 1 and/or 21 be found patentable, Applicants will be entitled to a rejoinder, and further examination, of these claims.

Election/Restriction

Applicants gratefully acknowledge the Examiner's decision to reconsider and reverse the previously made restriction between groups I (claims 1-5 10-16, 19, 20, and 49), and V (claims 21-25, 30-36, 39 and 40). As a result of this rejoinder and the various elections made in their last response, claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 have been examined on their merits.

Claims 3-5, 15, 16, 23-25, 35 and 36 are currently unexamined claims corresponding to unelected species that have not been withdrawn from consideration. Applicants respectfully note that, upon a determination that the elected species of "cisplatin" is found patentable, Applicants are entitled to a further search of the unelected species, which include "oxaliplatin", "ionizing/gamma radiation", "hydrogen peroxide" as found in examined claims 1 and 21, and further as found in corresponding unexamined dependent claims 3-5 and 23-25, will be entitled to examination. Applicants further note that, upon a determination that the elected species of

XPA "SEQ ID NO. 3" is found patentable, Applicants will be entitled to a further search of the unelected species XPA "SEQ ID NO. 4" as found in unexamined claims 15, 16, 35 and 36.

Applicants further note that claims 6-9, 17, 18, 26-29, 37, 38, and 41-48 have been withdrawn from consideration, but are related to the elected invention by linking claims 1 and 21. As discussed above, Applicants are entitled to rejoinder of these claims should linking claims 1 and/or 21 be found allowable. In particular, MPEP §809 states that "linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn...(and)...claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or includes all the limitation of the allowable linking claim must be rejoined and will be fully examined for patentability....". In this instance, Applicants respectfully note that claims 1 and 21 are properly generic claims in that they "include no material element additional to those recited in the species claims" (see MPEP §806.04(d)).

Further in this regard Applicants respectfully note that, while the Office Action relies upon MPEP §803.04 for the proposition that there is no strict requirement that more than one sequence be examined in an application, in fact, that section of the MPEP states that "normally ten sequences constitute a reasonable number for examination purposes...(and)...accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction" (emphasis added). Still further, Applicants note that MPEP §803.02, which addresses restriction practice for Markush style claims, such as Applicants' linking claims 1 and 21, clearly states that "if the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits." Furthermore, Applicants note here for the record that the members of the Markush group in claims 1 and 21 provide a common functionality in each of these method claims. The claimed use of alternative genes in the same step of the claimed method is thus readily distinguishable from an instance "where the case under consideration contains no disclosure of any commonality of operation function or effect" (see MPEP §806.04(e)).

Accordingly, Applicants believe the restriction requirement was in error, but, in any event, will be entitled to examination of claims 3-5, 15, 16, 23-25, 35 and 36 should the elected species be found patentable, and will be entitled to rejoinder of claims 6-9, 17, 18, 26-29, 37, 38, and 41-48 upon a finding that linking claims 1 and/or 21 are allowable.

Priority

The Office Action states that "Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §119(e)." In particular, the Office Action relies on 37 CFR 1.78 for the proposition that "a proper claim under 35 U.S.C. §119(e) must be made in the specification or in an application data sheet and must be made within the later of 4 months of filing of the non-provisional application or 16 months after the filing date of the provisional application."

In response to this action, and pursuant to the provisions of 37 CFR §1.78(a)(6) for acceptance of an unintentionally delayed claim of priority, Applicants have submitted with this response:

> (i) an amendment to the specification directing entry of a reference to the prior-filed provisional application, U.S.S.N. 60/194,343, filed April 3, 2000, thereby providing the reference required by 35 U.S.C. 119(e) and 37 CFR §1.78(a)(5) of this section;
>
> (ii) an authorization of payment of the surcharge set forth in 37 CFR §1.17(t); and
>
> (iii) a statement, accompanying payment of the surcharge set forth in 37 CFR §1.17(t), that the entire delay between the date the claim was due under 37 CFR §1.78(a)(5)(ii) and the date the claim was filed was unintentional.

Accordingly, Applicants respectfully request reconsideration of the effective filing date of the application and a determination that effective date corresponds to the date of filing of provisional application, U.S.S.N. 60/194,343, filed April 3, 2000.

Rejections under 35 U.S.C. §112 (enablement)

The Office Action states that claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 have been rejected under 35 U.S.C. §112, first paragraph, because "the specification, while being enabling for enhancing or potentiating the toxic effect of a cytotoxin on a cancer cell *in vitro* or *ex vivo*, does not reasonably provide enablement for performing the same method *in vivo*". Applicants respectfully traverse this rejection for the reasons that follow. As noted above, claim 49 has been cancelled, and the rejection of this claim has been thereby obviated.

First, Applicants respectfully note that the Office Action has selectively quoted references, which supposedly support the contention that "the specification is not considered to provide the requisite guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism." In particular, the Office Action cites Agrawal and Kandimalla ((2000) Mol. Med. Today 6: 72-81) for the proposition that there are "obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo*" and Jen and Gerwitz ((2000) Stem Cells 18: 307-19) for the proposition that there is a "problem" with antisense therapeutic delivery.

However, the sections cited from these references are not representative of their overall teachings. The mischaracterization of references as supporting a lack of enablement of the claimed invention and/or the selective use of passages from such references that carry the slightest negative tone is not a proper application of the appropriate legal standard for enablement, which requires a proper balancing of all the evidence (see *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995)). For example, the Agrawal and Kandimalla reference states, in prominent concluding statements, that "[m]any questions about the effects of antisense oligonucleotide sequence, secondary structures, cellular uptake, metabolism, excretion, tissue distribution, side effects and mechanism of action have been answered to a large extent, if not completely, in the past few years"...and further states that "antisense therapeutics can in fact be as simple as complementary base recognition....if proper design precautions and controls are used" (emphasis added).

Furthermore, the cited section of the Jen and Gerwitz on "Delivery" regarding the "efficiency" of delivery *in vivo* addresses something other than the legal standard for patentability and is, in any case, immediately followed by a discussion of various solutions developed to address the issue of efficient delivery. The other quotation taken from the Jen and Gerwitz reference that "efficient clinical translation of the antisense strategy has proven elusive" (emphasis added) again addresses a different standard than that required for patenting. Indeed, the cited section of the Jen and Gerwitz reference goes on to address FDA approval of certain antisense therapeutics that, in phase I and phase II trials, "have been characterized by a lack of toxicity but only modest clinical effects". Applicants respectfully note that, even if this comment that certain antisense therapeutics show "only modest" effects were truly representative of the field in general, it would still not support a lack of enablement of *in vivo* antisense therapeutics, because the standards for patentability are distinct from the standards of safety and efficacy required for FDA approval. Indeed, the Federal Circuit has made clear that "considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled" (citing *Scott v. Finney*, 34 F.3d (Fed. Cir. 1994), at MPEP 2164.05).

Accordingly, Applicants respectfully assert that the enablement rejection applies an erroneously strict legal standard for patentability that is supported by an unrepresentative sampling of the related art prior to the invention. Indeed, Applicants can cite numerous publications that support their assertion that the claimed method is enabled throughout its scope, including its *in vivo* therapeutic embodiments. For example Galderisi *et al.* ((1999) J. Cell . Physiol. 181: 251-7) specifically summarizes numerous studies demonstrating the therapeutic effectiveness of antisense oligonucleotides in the treatment of various diseases, including ovarian cancer using protein kinase C-alpha antisense.

Furthermore, Applicant respectfully note that the law of enablement provides that the *in vitro* results disclosed in the specification support enablement of the claimed *in vivo* methods. The Office Action states that "while the specification is enabling for enhancing or potentiating the toxic effect of a cytotoxin on a cancer cell *in vitro* or *ex vivo*, the specification is not enabling

for the broad claims of treating cancer in any organism (*in vivo*)". However, M.P.E.P § 2164.02 states:

> [a]n in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. . . . In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition (citing *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

This section further states that a "rigorous or an invariable exact correlation is not required . . .."

In the instant case, Applicants' specification provides extensive *in vitro* evidence for enablement of the claimed invention, and, furthermore, provides support for the *in vivo* therapeutic embodiments of the claimed invention. For example, Examples 2-4 on pages 30-32 demonstrate the effectiveness of the claimed method using XPA antisense oligonucleotides to potentiate or enhance the toxic effect of the cytotoxins cisplatin and oxaliplatin on cancer cells. Furthermore, the application provides ample guidance for the skilled artisan to apply the claimed method in *in vivo* therapeutic embodiments. For example, beginning at page 21, line 18 the specification provides support for effecting *in vivo* cancer treatment with the claimed invention, including methods of administration, pharmaceutical compositions for effective *in vivo* delivery, therapeutic doses, and treatment schedules for both the claimed antisense oligonucleotides and the cytotoxic agents that they potentiate or enhance. Accordingly, Applicants respectfully assert that the claimed invention is enabled throughout its scope, including both *in vitro* and *in vivo*

embodiments, because the claims are not overly broad and are supported in their full scope by the examples and further teaching of the specification.

Accordingly, reconsideration and withdrawal of the rejection for lack of enablement is respectfully requested.

Rejections under 35 U.S.C. §112 (written description)

Claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Office Action cites the recent decision in *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004) for the proposition that merely describing methods of screening for compounds to identify those that might support a claimed method of treatment is inadequate "written description" support for a method of treatment claim that requires the use of those compounds, which would be identified in such a screen for compounds having a desired inhibitor activity. In this regard, the Office Action particularly notes the Court's statement that "without such disclosure,"...(*i.e.*, of the structure of compounds that are active in the screen)....."the claimed methods cannot be said to have been described". Applicants respectfully traverse this rejection for the reasons which follow. As noted above, claim 49 has been cancelled, and the rejection of this claim has thereby been obviated.

As an initial matter, Applicants respectfully note that there exists a strong presumption that an adequate written description of the claimed invention is present when the application is filed (see MPEP §2163 I. A., citing *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976)). Furthermore, the written description requirement imposes no predetermined standard for a number of actual working examples that must be disclosed as is implied in the Office Action when it states, at page 14, "the specifically disclosed structures of antisense sequence oligonucleotides capable of inhibiting XPA expression are not sufficient to describe the full breadth of the claimed genus". Indeed possession of the invention may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" *Amgen, Inc.v. Chugai Pharmaceutical*, 927 F.2d 1200 (Fed. Cir. 1991) (stating a compound may be described by "whatever characteristics sufficiently distinguish it").

Furthermore the standard for fulfilling the requirement is a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." (see, *.e.g., Enzo Biochem., Inc. v. Gen-Probe, Inc.*, 323 F.3d 9565 (Fed. Cir. 2002).

Accordingly, the Applicants disclosure of multiple function antisense oligonucleotides, coupled with a description of the complete nucleotide sequence of the targeted transcripts and the knowledge of the skilled artisan in designing still other active antisense oligonucleotides that are complementary to these targeted transcripts (see Agrawal and Kandimalla (2000) Mol. Med. Today 6: 72-81), provides adequate written description so that the one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (see, *e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003)).

Indeed, Applicants aver that the instant application is readily distinguishable from the situation in the *Univ. of Rochester* case cited in the Office Action. In particular, the instant application discloses multiple operable compositions for use in the claimed method of treatment (e.g., the XPA antisense oligonucleotide HYB 963 (SEQ ID NO. 3), amongst others). Furthermore, contrary to the statement in the Office Action that "the skilled artisan cannot envision the detailed structure of the encompassed antisense sequences", further additional such structures are fully capable of being envisioned by a person of skill in the art, as was addressed above.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112 for lack of written description is respectfully requested.

Rejections under 35 U.S.C. §102

The Office Action states that claims 1, 2, 10, 19-22, 30, 39, 40, and 49 have been rejected under 35 U.S.C. §102(b) as being anticipated by Lu *et al.* (abstract dated March 2000 by Yi Lu, Sridhar Mani, Sudhir Agrawal, and David B. Bregman "Mixed Backbone Oligonucleotides Targeting the Nucleotide Excision Repair Protein XP Potentiate Cisplatin Cytotoxicity" Proc. Amer. Assoc. Can. Res. 41: 643).

Applicants respectfully traverse this rejection as obviated by the above-made petition to obtain the benefit of their earlier provisional filing date under 37 CFR §1.78(a)(6). In particular, upon acceptance of their petition, Applicants effective priority date will correspond to the date of filing of provisional application, U.S.S.N. 60/194,343, filed April 3, 2000. Applicants note that, regardless of the actual date that the Lu *et al.* abstract became public and regardless of the actual content of the Lu *et al.* disclosure, the Lu *et al.* abstract published on a journal page that is labeled "March 2000". This date is clearly less than a year before the perfected priority date of the instant application. Accordingly, the Lu *et al.* abstract is not a §102(b) reference, because it is clearly not "a printed publication...more than one year prior to the date of the application for patent in the United States." Therefore reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Furthermore, again regardless of the actual date that Lu *et al.* actually became available to the public and its actual content, it is also not prior art to the claimed invention under 35 U.S.C. §102(a) because it is not a printed publication "by others" "before the invention thereof by the applicant for patent". In particular, the Lu *et al.* abstract is authored by Yi Lu, Sridhar Mani, Sudhir Agrawal, and David B. Bregman, all of whom are named inventors in the instant application. Accordingly, the Lu et al. abstract is not §102(a) art because it is not "by another".

Therefore the Lu et al. abstract is not prior art under 35 U.S.C. §102, and so reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103

Claims 1, 2, 10, 11, 14, 19-22, 30, 31, 34, 39, 40 and 49 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Tortora *et al.* ((1997) Proc. Natl. Acad. Sci USA 94: 12586-91) in view of Koberle *et al.* ((1999) Curr. Biol. 9: 273-6) and Horton *et al.* ((1995) Nucl. Acid. Res. 23: 3810-15). In particular, the Office Action states that "it would have been obvious to a person of ordinary skill in the art at the time of the invention to modify the teachings of Tortora *et al.* that antisense inhibition of gene expression has a synergistic effect with cisplatin in cancer cells by targeting the XPA gene." Applicants respectfully traverse this rejection for the

reasons which follow. As noted above, claim 49 was cancelled above and so Applicants rebuttal is directed at the remaining rejected claims 1, 2, 10, 11, 14, 19-22, 30, 31, 34, 39, and 40.

First, the Tortora *et al.* reference fails to teach or suggest "an oligonucleotide complementary to...Xeroderma pigmentosum group A (XPA) gene" as required by claims 1 and 21 and claims 2, 10, 11, 14, 19, 20, 22, 30, 31, 34, 39, and 40 from which they depend. Rather, the Tortora *et al.* teaches the inhibition of protein kinase A type I by antisense oligonucleotides targeting its RIα regulatory subunit. Nothing in Tortora *et al.* would teach or suggest the claimed method requiring an antisense oligonucleotide directed to the XPA gene.

Furthermore, this deficiency in the teaching of Tortora *et al.* is not made up for by the teachings of the Horton *et al.* reference. In particular, the Horton *et al.* reference describes the use of a vector producing an antisense transcript that is complementary to a completely different target, a DNA polymerase beta (beta-pol) gene. Nothing in Horton *et al.* would teach or suggest the claimed method of targeting the XPA gene with an antisense oligonucleotide to achieve a potentiation or enhancement of the toxic effect of a cytotoxin such as cisplatin. Still further, none of the supposed technical problems in allowing the skilled artisan to make and use the claimed invention using antisense oligonucleotides, as raised in the earlier §112(enablement) rejection of the Office Action, are addressed by either the Tortora *et al.* or the Horton *et al.* reference.

Still further, these deficiencies in the teaching of Tortora *et al.* and Horton *et al.* references are not made up for by the Koberle *et al.* reference. Indeed the Koberle *et al.* reference does not teach an antisense oligonucleotide at all, let alone an XPA antisense oligonucleotide as required in the method of the claimed invention. Applicants themselves drew attention to the Koberle *et al.* reference in their description of the background of the invention (see page 4, line13). While the Koberle *et al.* references addresses a possibly unique role of the XPA protein in testicular germ cell tumor extracts, there would be no reasonable expectation of success of making and using the claimed invention of treating a cancer cell because, as Koberle *et al.* emphasizes, testicular germ cell tumors behave differently from most other forms of metastatic cancer (see first two sentences of the abstract). Furthermore even if the Koberle *et al.*

reference did teach or suggest the use of XPA antisense oligonucleotides, which it does not, it still does not address any of the aforementioned supposed technical problems in allowing the skilled artisan to make and use the claimed invention.

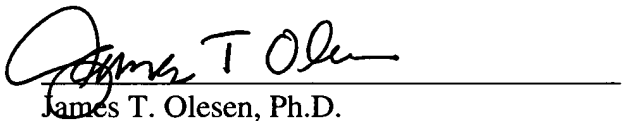
Accordingly neither Tortora *et al.*, Horton *et al.* or Koberle *et al.*, alone or in any combination, teach or suggest the claimed method of the invention. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

The time for responding to this action has been extended to March 14, 2005 by the accompanying Petition for a Three Month Extension of Time and payment of fee. Applicants believe no other fees are due in connection with this Amendment. However, if there are any fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,



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Dated: **March 14, 2005**

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